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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/961,443	10/30/1997	TIM M. TOWNES	04005/013003	7598

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/961,443	Applicant(s) TOWNES ET AL.	
	Examiner Deborah Crouch	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The request filed on April 10, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/961,443 is acceptable and a CPA has been established. An action on the CPA follows. The declarations by Townes, declarations I and II, have been considered but are not persuasive. The reasoning is provided in the text of the enablement rejection below. Applicant mentions a Stice declaration in their response, but no such declaration can be found in the file (response, April 10, 2002, page 4, line 3).

Claims 1-24 are pending. However, claim 20 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention. Election was made without traverse in a paper no. 8. Claims 1-19 and 21-24 are under current examination.

Applicant's filing of a substitute oath is acknowledged

The abandonment of application 08/934,385 has overcome the statutory and obviousness type double patenting rejection made in the previous office action.

Claim Rejections - 35 35 USC § § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

Claims 1-19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "transgenic mouse whose genome comprises a human LCR γ-β hemoglobin switching DNA construct, wherein said genome is further homozygous for murine α- and β-globin knockout alleles such that said knockout alleles result in said mouse failing to synthesize murine hemoglobin, and wherein said hemoglobin switching construct is expressed such said mouse develops hemolytic anemia", does not reasonably provide enablement for a transgenic nonhuman mammal comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said nonhuman mammal." The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With regard to the scope of the claimed invention, Applicant's claims are directed to transgenic non-human mammals whose genome comprises knockout mutations in endogenous globin genes, and the insertion of human globin genes into the mouse's genome. As such, the specification discloses the technology of making transgenic mice utilizing embryonic stem (ES) cells.

Applicant argues, with regard to the enablement of non-mouse mammals, that at the time of the priority application, March 6, 1996, that non-human mammals could be made by nuclear transfer. Applicant argues that nuclear transfer provides the ability to culture cells, comprising genetic manipulations such as knockout technology, and that the manipulated cells can then be used to generate whole animals. Applicant further argues that not a single claims requires the introduction of a knockout construct into an ES cell. Applicant states that the claims do not contain this limitation as they can be made by other means as stated in the Townes declaration 1. Applicant argues that since they were the first to produce the animal, that they do not need to teach all ways to make such an animal, and all that is required is that the artisan be able to produce the animal by any method. Applicant reiterates that those skilled in the art could have made the animals by nuclear transfer as stated in Townes Declaration 1. Applicant argues that what is required to make cells containing the alpha and beta globin constructs is the ability to culture cells, which then can be used to produce a whole animal. Applicant argues that Dr. Townes stats that as of January 1996, the relevant scientific community knew how to culture donor cells, manipulate the cells by knockout technology, and perform nuclear transfer (Townes Declaration 1). Applicant argues that Dr. Townes states that with the instructions provided in Wilmut, that one who produces whole animals from cultured cells would be able to make a non-mouse mammal based on the present specification. These arguments are not persuasive.

A review of both Campbell references reveals that neither contemplated using nuclear transfer for the production of transgenic or knockout mammals. As the specification did not suggest such nuclear

transfer for the production of the claimed mammals, and the art at the time of filing did not teach nuclear transfer for the production of transgenic mammals, then applicant cannot post-filing reach back and assert that one reading the specification would know to use nuclear transfer to produce transgenic or knockout mammals. With particular regards to declarant's statements regarding nuclear transfer as of January 6, 1996, it is noted that Campbell, exhibit 2, provides evidence that successful sheep production was problematic and that prior attempts with cultured cells had failed. Campbell states that they had success in producing sheep when primary embryonic disc cells were used up to passage 3, but that at passages 6 and 10, the embryonic disc cultures failed to produce sheep. Campbell states that cultured 9 day embryonic disc cells, but there is no indication of at which passage the donor cell were, that had been made quiescent, gave rise to cloned sheep embryos. If anything Campbell teaches that there is a great degree of unpredictability in the art of nuclear transfer, and that the cell type and its culture history is critical to a successful outcome. Further Campbell only produces embryos, and not sheep. The second Campbell reference, exhibit 1, produces sheep by nuclear transfer where sheep blastomeres, and not cultured cells were used as donors (page 1386, col. 2, parag. 1). Declarant's statements and applicant's arguments center around modifying cultured cells. However, neither reference states or discusses the production of transgenic sheep by nuclear transfer. Thus the examiner does not agree that the art at the time of filing teaches the production of mammals by nuclear transfer of modified nuclei.

Applicant is limited to knockout technology as that is the only means enabled by the specification to produce the claimed transgenic mammals. There are no other means of preventing disruption of the endogenous alpha and beta globin genes other than their disruption. The specification provides no other guidance to obtaining mice or mammals not expressing the endogenous genes. Thus, the methodology of the specification is the only guidance that the artisan would have before them. Therefore, it is appropriate to examine the methodology through which the mammals are taught to be made and determine if it enables the full scope of the claim. While applicant need not teach multiple methods of making a product, the method taught has to be enabled for the breadth of the claimed invention.

Applicant argues that Moreadith's reference to putative ES cells is more of an indication that these cells have not been shown to contribute to the germ line rather than an inability of these cells to do so. Applicant argues that these cells may be formed into whole animals after manipulation. Applicant argues that Seamark states that nuclear transfer is "under active consideration." Applicant argues that nuclear transfer technology was not "putative" or "hoped" as it existed in working form in 1994. Applicant argues that Mullins teaches that ICM cells injected into blastocyts have been shown to contribute to the germ line, and the totipotency of the ICMs have been shown to produce offspring after transfer into enucleated oocytes. Applicant argues that Mullins, like Seamark, provide evidence that ES cell technology for other mammals existed at the time of filing, and that nuclear transfer technology was also available. These arguments are not persuasive.

The "putative pluripotential ES cell lines" stated by Moreadith had not been shown at the time of filing to be totipotent ES cells, the type required to make a null mutant mouse as claimed. The availability of totipotent ES cells to implement the claimed invention according to the guidance in the specification requires totipotent ES cells. Applicant has not provided any evidence that these other mammalian putative ES cells were later shown to be totipotent. That these cells had not been shown to totipotent is the crucial factor here. Essential elements for the implementation of the claimed invention must be readily available to the public at the time of filing. As for Seamark, the statement is that nuclear transfer is "under consideration", and not a current option. Seamark clearly states that the efficiency of nuclear transfer is low, and indicates that such a problem for the procedure. Seamark continues to state that the methodology is being investigated to improve the techniques so that nuclear transfer becomes a reasonable alternative. (see page 655, col. 1). Seamark goes on to discuss the difficulties in obtaining pre-implantation embryos by describing conditions known that affect pre-implantation growth (page 655, col. 2 to page 655, col. 3). Mullins states that at the present time, 1996, nuclear transfer techniques are potentially very useful for the production of cloning offspring, but that the reliable generation of bovine ES cells require the pooling of ICM's from several blastocysts and that further efforts are needed to enable

the long term culture of clonal bovine ES cells. Mullins goes on to state that several chimeric animals have been generation for several species but none have shown germline transmission, other than the mouse. Thus, while Seamark and Mullins suggest that nuclear transfer techniques would obviate several problems, neither indicate that nuclear transfer is a readily available option at the time of filing to produce knockout mammals.

Further, applicant's arguments are not clear as a nuclear transfer method has not been provided in either the response or the art. For example, which cells by which method does applicant propose to insert the knockout construct? As for nuclear transfer as routine method, the art teaches that the particular methodology must be determined for each species, and that such methodology is not necessarily transferable from one specie to another. In regard to this, Westhusin (2001), summarizes the art at the time of filing as teaching that one of the major factors influencing a successful cloning out come is species of target animal. Westhusin goes on to state that while the basic methodology for nuclear transfer may be similar, the specific materials and methods do not automatically apply across all species. Westhusin outlines six factors which contribute to successful cloning: 1) acquisition of mature ova, 2) removing the chromosomes contained within the ova, 3) transfer of cell nuclei obtained from the animal to be cloned into enucleated ova, 4) activation of the newly formed embryo, 5) embryo culture in vitro, and 6) transfer of the cloned embryo into a surrogate mother. Westhusin further states that each of these steps will vary slightly between species, but that, more importantly, the efficiency of each step varies among species, ultimately affecting the ease of which a particular animal can be cloned. (see Westhusin (2001) Theriogenology 55, page 36-37, bridg. parag.). This analysis is supported by Polejaeva (2000) that states, in regard to the inefficiency of cloning, that several factors affect the inefficiency: laboratory to laboratory variation, oocyte source and quality, methods of embryo culture, donor cell type, possible loss of somatic imprinting in the nuclei of the reconstructed embryo, failure to reprogram the transplanted nucleus adequately, and failure of artificial methods of activation to emulate reproducibly those crucial membrane-mediated events that accompany fertilization (Polejaeva (2000), page 1, parag. 2). Thus nuclear transfer is

not routine, but requires extensive experimentation without a predictable degree of success. This is emphasized by Pennisi and several scientists working in the area of mammalian cloning point to a lack of general and reproducible success. Robert Wall of the USDA is quoted as stating that despite years of effort, "[w]e're in the same bind that we've always been in. A majority of [would be clones] do not make it to term." (Pennisi and Vogel (2000), page 1722, col. 1, parag. 2, lines 9-14). Pennisi and Vogel state that "even when an embryo does successfully implant in the womb, pregnancies often end in miscarriages" (Pennisi and Vogel (2000), page 1722, col. 1, parag. 3, lines 16-18). Attempts to clone pigs using techniques successful in sheep were not successful, indicating that cross-species application of methodology is unpredictable (Pennisi and Vogel (2000), page 1725, col. 1-2, bridg. parag.). The case with rabbits indicates that obtaining an embryo by nuclear transfer does not translate into a cloned rabbit. While many cloned rabbit embryos can be made, they abort upon transfer to surrogate mothers, and in 2000, there had not been any successes in cloning rabbits (Pennisi and Vogel (2000), page 1725, col. 2, parag. 3). With primates, two cloned monkeys were produced, but there has been no subsequent successes in primate cloning (Pennisi and Vogel (2000), page 1726, col. 2, line 6 to col. 3, line 3). With specific regard to cats, there is no report of a successful birth of the cloned cat embryo implanted into a surrogate female cat. However, two subsequent attempts to implant cat eggs or reconstructed embryos failed, providing for an unpredictable outcome for cat cloning (Pennisi and Vogel (2000), page 1726, col. 2, parag. 3, lines 4-5). Others have reported establishing pregnancies but no report of a cloned cat being born, and these researchers do not suggest when such an event might occur (Pennisi and Vogel (2000), page 1726, col. 2, parag. 3, lines 5-9 and 11-12). As the authors state, establishing pregnancies is only part of the problem and is not a guarantee of a cloned cat being produced (Pennisi and Vogel (2000), page 1726, col. 2, lines 9-11). Thus, applicant's arguments that the claimed mammals could be made by nuclear transfer is not persuasive because it is not clear from the arguments the protocol for inserting the construct(s) into what cells, and that the art generally regarded nuclear transfer as unpredictable.

Applicant argues and declarant Townes 2 states that transgenic expression of a hormone is very different and not predictive of expression of an intracellular hormone. Applicant further argues that the art cite by the examiner is not relevant for the present subject matter. Declarant Townes 2 has supplied abstracts showing that the expression of human hemoglobin was not deleterious in pigs.

The examiner agrees with applicant and withdraws this portion of the enablement rejection. The difference between the pigs in the prior art and those presently claimed is that the presently claimed pigs are lacking their endogenous alpha and beta globin genes. This is not seen as an obstacle to expression of human hemoglobin. Thus, Hammer et al, Ebert et al, Strojek and Wagner and Kappel et al are withdrawn. Mullins et al and Wall et al are also withdrawn to the extent that they relate to the unpredictable expression of a trangene in transgenic mammals. Thus applicant's arguments in section 2, pages 8-12 of the response filed April 10, 2002 are persuasive.

Applicant argues and Declarant Townes 2 states that switching is not needed for all hemoglobin transgenes. Declarant states that they used a construct that switches from fetal to adult beta globin in their model of sickle cell anemia. This argument is not persuasive.

The broader claims encompass those situation where there is a need or desire in the mammal to have the switch from fetal human. Also certain claims state that the hemoglobin contains a sickle cell mutation.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-19 under 35 U.S.C. 103(a) as being unpatentable over Paszty et al (Ref. Q or paper no. 5) and Ciavatta et al (Ref. G of paper no. 5) taken with Rubin et al (Journal of Clinical Investigation, 1991) and Fabry et al (Ref. I of paper no. 5) is overcome by the statement of Declarant

Townes 2, parag. 8, that mice only expressing human hemoglobin would not have been predicted to survive because of great oxygen needs of the high metabolic rate of the mouse, and differences in oxygen affinity.

Although, applicant provided no arguments to this rejection, the rejection of Claims 21-24 under 35 U.S.C. 103(a) as being unpatentable over Paszty et al and Ciavatta et al taken with Rubin et al and Fabry et al, as applied to claims 1-91 above, and further in view of Westphal (FASEB J, 1989) is overcome by the statement of Declarant Townes 2, parag. 8, that mice only expressing human hemoglobin would not have been predicted to survive because of great oxygen needs of the high metabolic rate of the mouse, and differences in oxygen affinity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Deborah Reynolds, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Zeta Jones, whose telephone number is (703) 305-3291.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
May 31, 2002